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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/235,986	01/22/99	HENDRICKSON	W 58323/JPW/PT

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EXAMINER

LUNDGREN, J

ART UNIT	PAPER NUMBER
1631	11

DATE MAILED: 12/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/235,986

Applicant(s)

HENDRICKSON ET AL.

Examiner

Jeffrey Lundgren

Art Unit

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 November 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____

DETAILED ACTION

1. The amendment submitted by Applicants on November 14, 2000, has been considered and entered. The final rejection mailed on May 31, 2000, has been withdrawn for the reasons below.

Claim Rejections - 35 USC § 103

2. The rejection of claims 1, 3, 5-7, 9, and 11-12, under 35 U.S.C. 103(a) as being unpatentable over Bachar et al. (Protein Engineering 6, 279-288, 1993), in view of Hendrickson et al. (The EMBO Journal 9, 1665-1672, 1990), in the Office Action mailed on June 9, 2000, is withdrawn for the reasons argued by Applicants in the response received on November 14, 2000.

3. The rejection of claims 4 and 10, under 35 U.S.C. 103(a) as being unpatentable over Bachar et al., and Hendrickson et al., as applied to claims 1, 3, 5-7, 9, and 11-12, above, and further in view of Lima et al. (Structure 5, 763-774, **1997**), in the Office Action mailed on June 9, 2000, is withdrawn for the reasons argued by Applicants in the response received on November 14, 2000.

4. The rejection of claims 2 and 8, under 35 U.S.C. 103(a) as being unpatentable over as applied to claims 1, 3, 5-7, 9, and 11-12, above, and further in view of Craig et al., (U.S. Patent No. 5,525,198, June 11, 1996), in the Office Action mailed on June 9,

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2000, is withdrawn for the reasons argued by Applicants in the response received on November 14, 2000.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 7 are indefinite for reciting the term "known structural information functional information", as the skilled artisan would not be able to determine which the metes and bounds of this limitation (see page 10, lines 10-27 of the instant specification).

Claims 1 and 7 are indefinite for reciting the phrase "corresponding homologous sequence information", as it is not clear which sequences which sequence would be determined to have "corresponding homology" and the sequences that do not, as would be reasonable for establishing the families.

Claims 1 and 7 are indefinite for reciting the phrase "appropriately representative", as neither the claims nor specification define which members are appropriately representative, and those members of the family that are not appropriately representative.

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Claims 1-2 and 7-8 are indefinite for using the generic pronoun "ones" to refer to a previously established limitation. An amendment replacing the term "ones" with the specific limitation which already has proper antecedent basis would overcome this rejection.

Claims 1 and 7 are indefinite for reciting the phrase "...that are effective as proteins", as it is not clear with respect to the manner in which a synthesized protein would not be an "effective" protein.

Claims 1 and 7 are indefinite for reciting the phrases "predetermined diffraction characteristics" and "suitable" in determining which crystal are of reasonable quality for x-ray diffraction measurements as the skilled artisan would not reasonable be able to determine the metes and bounds of these limitations. Page 16 of the instant specification speaks to the general steps of preparing crystals, yet there is no guidance for the suitable determination step.

Claims 1 and 7 recite the limitation "other known three-dimensional structures". There is insufficient antecedent basis for this limitation in the claim. For example, this phrase assumes that a three-dimensional structure has already been established for the target, however, Applicants have not clearly set forth in the method the point where the three-dimensional structure has become "known" or determined.

Claims 1 and 7 are indefinite for reciting the limitation "known" in reference to the known three-dimensional structures stored in the databases, as it is not clear how this factor is "known". An amendment deleting the term "known" would overcome this rejection.

Claims 1 and 7 are indefinite for reciting the phrase "homology model", as the skilled artisan could not reasonably be able to determine the metes and bounds of the model (i.e., what the essential parameters are, and their relationships to one another).

Claims 1 and 7 are indefinite for reciting the phrase "along with" as a means to describe a step carried out with a bioinformatics tool and the developed homology model. An amendment replacing the phrase "along with" using the term "and" would overcome this rejection.

Claims 7 is indefinite for failing to recite a final process step which agrees back with the preamble. While minor details are not required in method/process claims, at least the basic steps must be recited in a positive, active fashion. See *Ex parte Elrich*, 3 USPQ2d, p. 1011 (Bd. Pat App. Int. 1986). For example, claim 7 is drawn to a method of determining experimentally a plurality of three-dimensional atomic structures, yet the claim recites a final step of developing a homology model using computational tools.

Claims 6 and 12 are indefinite for reciting the phrase "more appropriate constructs", as the skilled artisan would not have reasonable guidance in determining this limitation.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 3, 5-7, 9, and 11-12, are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachar et al. (Protein Engineering 6, 279-288, 1993), in view of Hendrickson et al. (The EMBO Journal 9, 1665-1672, 1990), in view of Everett et al. (Nature Genetics 17, 411-422, **1997**), in view of Andrea et al. (J. Med. Chem. 34, 2824-2836, **1991**).

Claims 1, 3, 5-7, 9, and 11-12, are drawn to a system and process for determining experimentally a plurality of three-dimensional atomic structures, each associated with a corresponding protein, first a protein database of sequence information and known structural and functional information which is systematically organized, must be established for integration with at least one bioinformatics tool using the structural and functional information to cluster the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences. Afterwards, the analysis of the target protein using sequence of the

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information corresponding to other family members of the database and information corresponding to other known three-dimensional structures which is stored in the database, with means for refining the model for functional motifs, and means for defining at least one class of compound predicted to have binding potency using the active site information.

Bachar teaches a method/system for protein classification, wherein an experimentally-derived, three-dimensional structure of a target protein can be classified by assignment to a cluster set of structurally similar, three-dimensional representation of proteins in an organized database. The design and organization of the database consists of three major steps: 1) finding relatively small subset of the structures that form an initial match; 2) finding clusters of initial matches that represent similar transformations; and 3) extending the clusters to contain additional matching pair residues. These steps are further comprised of sub-steps detailed in the disclosure (pages 280-283). As a result of organizing a database and developing a means to utilize the database for similarity comparisons/clustering, one can determine a surface motif in a target protein, one can determine an activity of a given compound to the target protein, and one can objectively determine a number of chemical or biological properties of the target protein, such as active sites, surface properties, cores, etc., (see *Conclusions*).

Although Bachar utilize data which represent the three-dimensional structures of proteins, the investigators do not disclose a means for preparing proteins, a means of preparing protein crystal for analysis, a means of three-dimensional analysis, or any

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peripheral mean for data acquisition. Bachar does not specifically teach the use of sequence information for classification, or compound classification to the clustered proteins.

Hendrickson et al., teach a system and process for incorporating selenomethionine (as a replacement for methionine) into recombinant proteins produced from plasmids in *E. coli.*, which are crystallized and analyzed by multiwavelength anomalous diffraction (MAD) as a means for producing a three-dimensional representation of a target protein. Their method provides the advantages over conventional x-ray techniques for elucidating three-dimensional protein structures, in that MAD utilizes the scattering effects of resonance between x-rays and bound atomic orbitals, it is perfectly isomorphic, allows for data sampling from a single crystal, and the analysis is algebraically exact (see *Introduction*).

Everett discloses a method/system for characterizing/clustering proteins into families based on their sequence and structure, such as using their linear sequence and by characterizing transmembrane regions using PHDhtm (see *Computational analysis of PDS and its encoded protein*). Everett then assigns a function to an unknown protein based on the similarity comparison of the target protein to the proteins which have been clustered into families which also have functional information. For example, a function of sulfate transport is assigned to pendrin based on the family clustering model which classified pendrin in the family of other sulfate transporters, and the observed physiological effects that are present which correlate with sulfate transport deficiency in those diagnosed with Pendred syndrome (see PDS mutations in Pendred-syndrome

families). Everett discloses that these bioinformatics tools are advantageous in that they reduce experimental efforts of trial and error, wherein researchers would otherwise be uncertain of the target protein's function (see *Discussion*).

Andrea discloses a method/system for clustering objects in multi-dimensional space as a means of characterizing the binding relationships between a proteins a chemical compounds in a database through quantitative structure-activity relationships, QSARs (see entire document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize sequence and structure data as taught by Everett, with the method of Bachar¹ as a means to more selectively determine proteins of interest based on a given or suspected function, before utilizing the protein structural determination means as taught by Hendrickson (i.e., selenomethionyl protein expression technique for MAD analysis because of the aforementioned advantages of using their method/system for recovering data sets representing the three-dimensional structure of proteins over conventional x-ray crystallographic methods). Bachar discloses that although sequence-based classification schemes are not flawless, these methods can prove to be quite useful in protein family classification, and would be improved upon if applied to the sequence-independent method for three-dimensional structural refinement (see page 286, second and third paragraphs). One would recognize that the refined model and structure of the experimentally examined protein would provide an improved and refined overall model, and the physicochemical features of the refined target protein

¹ The method of Bachar requires three-dimensional data of the target protein.

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whose structure has been determined could be applied to the other protein family members which were originally classified based on sequence information. One of ordinary skill in the art would also be motivated to implement the QSARs methodology as disclosed by Andrea, as a means to determine which chemical structures (or family of chemical structures) associate with a given protein structure (or family thereof). Therefore, the invention as a whole was *prima facie* obvious at the time the invention was made.

10. Claims 4 and 10, are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachar, Hendrickson, Everett, and Andrea, as applied to claims 1, 3, 5-7, 9, and 11-12, above, and further in view of Lima et al. (Structure 5, 763-774, **1997**).

Claims 4 and 10, are drawn to the system and process of claims 1 and 7, respectively, wherein the synchrotron storage ring has undulator beamlines for use with MAD.

Neither Bachar et al., nor Hendrickson et al., teach a synchrotron storage ring which has undulator beamlines for use with MAD.

Lima et al., teach using an undulator beamline x-ray source, with MAD because of the high output levels, with narrow, tunable, harmonic peaks (see *Results and Discussion*).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the undulator beamline x-ray source, in place of the synchrotron device as taught by Hendrickson et al., because Lima et demonstrate of a

high output x-ray source, with narrow, tunable, harmonic peaks. Therefore, the invention as a whole was *prima facie* obvious at the time the invention was made.

11. Claims 2 and 8, are rejected under 35 U.S.C. 103(a) as being unpatentable over Bachar, Hendrickson, Everett, and Andrea, as applied to claims 1, 3, 5-7, 9, and 11-12, above, and further in view of Craig et al., (U.S. Patent No. 5,525,198, June 11, 1996).

Claims 2 and 8, are drawn to the system and process of claims 1 and 7, respectively, wherein a cryogenic freezing means is used to freeze the target protein crystal.

Neither Bachar et al., or Hendrickson et al., disclose the use of cryogenic freezing means to freeze the target protein crystal.

Craig et al., teach the cryogenic freezing of target protein crystals as a means of increasing the crystal's stability during exposure to x-ray sources (column 5, lines 3-18).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a means for the cryogenic cooling of the target protein crystal, with the system/process of Bachar et al., in view of Hendrickson et al., as Craig et al., teach that cryogenic cooling preserves crystals during x-ray sampling. Therefore, the invention as a whole was *prima facie* obvious at the time the invention was made.

Conclusion

12. No claims are allowable.

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13. Any inquiry concerning the *merits* of this communication or earlier communications from the Examiner should be directed to Jeffrey S. Lundgren whose telephone number is (703) 306-3221. The Examiner can normally be reached on Monday-Friday from 7:00 AM to 5:00 PM (EST).

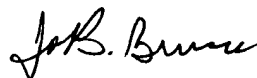
If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Michael Woodward, can be reached at (703) 308-4028.

Any inquiries of a *general* nature relating to this application should be directed to the Patent Analyst for Art Unit 1631, Ms. Pauline Farrier, whose telephone number is (703) 305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1631 using (703) 308-0294. Please notify the Examiner of incoming facsimiles prior to sending papers to the aforementioned fax number. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).



Jeffrey S. Lundgren, Ph.D.



JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER